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COMPLETE SPECIFICATION

Tannates of Morphine Alkaloids

We, IRWIN, NEISLER & Co., a Corporation organised and existing under the Laws of the State of Illinois, United States of America, of Decatur, State of Illinois, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to tannate compositions of morphine alkaloids and is more particularly concerned with tannates of the morphine alkaloids wherein the ratio of alkaloid to tannic acid is about $5 \pm 1/2 : 1$.

The term morphine alkaloids is used with reference to morphine and its simple derivatives or modifications as hereinafter defined which are used as components of analgesic and antitussive preparations. The tannates are prepared from tannic acid N.F. which is considered to be essentially a pentadigallyl ester-like compound of glucose, that is penta-(digallyl)-glucose which has the idealized formula $C_{76}H_{52}O_{46}$.

Morphine alkaloids include some of the most valuable analgesic and antitussive compounds known. One of the limitations in the effective use of morphine and some of its derivatives by the oral route is the relatively short duration of action of the drugs. Morphine itself, for example, is rather quickly inactivated in the animal organism and rapidly absorbable salts of the drug have a relatively short duration of action. One of the objects of the present invention is to provide an oral composition containing morphine alkaloids in such form that the drug is released gradually over a prolonged period of time thereby to provide an extended duration of action of the drug without inducing the undesirable side reactions which result from over-dosage.

Although tannins have been known to form precipitates with alkaloids, morphine alkaloid tannates of reproducible compositions and properties are new entities which permit safe application of these preparations in oral therapy. Penta-(digallyl)-glucose has five galloyl-gallic acid residues and it is apparent that in forming salts, a multiplicity of proportions ranging from 1 to 5 moles of alkaloid base per mole of tannic acid may be present. In other words, there theoretically are five possible morphine alkaloid tannate salts; one in which there is a mole of morphine alkaloid present for each of the five galloylgallic acid residues or 5 moles of morphine alkaloid per mole of tannic acid (this is the preferred salt of the present invention); one in which there is a mole of morphine alkaloid present for only one of the five galloylgallic acid residues or one mole of morphine alkaloid per mole of tannic acid; and the in-between situations, where there are two, three or four moles of morphine alkaloid present per mole of tannic acid. The 5 to 1 ratio of morphine alkaloid to tannic acid provides the most desirable composition of the various possible morphine alkaloid tannates.

The preferred tannates of the invention are the penta-morphine, penta-codeine and penta-dihydrocodeine salts of penta-(digallyl)-glucose, said salts being substantially free of other morphine-, codeine- and dihydrocodeine-complexed tannins.

It is a feature of the invention to combine these tannates with suitable excipients to form oral sustained release compositions for administration in unit dosage form.

It should be appreciated that the various tannate salts are actually molecular complexes, so that the ratios involved may not statistically be whole numbers, but may involve fractions. This is because, while any single molecule of complex has an exact whole number ratio, if one had an equal number of 5 to 1 and 4 to 1 complexes, a composition would be provided which would be statistically reported as a $4\frac{1}{2}$ to 1. Further there are practical limits to the accuracy of the analytical methods, the uniformity of various

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lots of N.F. tannic acid and minor variations in preparative procedures, wherefore the 5 to 1 ratio is given rather as $5 \pm \frac{1}{2}$ to 1.

The term "morphine alkaloids" as used herein, means methyl morphine (codeine), methyl dihydromorphine (dihydrocodeine), dihydrocodeinone, 6-methyldihydromorphinone and ethyl morphine.

The various morphine alkaloid tannate salts may be prepared as follows: The alkaloid is dissolved in a small volume of an alcohol, e.g., methyl, ethyl or propyl alcohols. For each molar equivalent of base, there is added 374 grams of tannic acid N.F. in a solution of this alcohol. This represents a 10 per cent excess of one-fifth the molecular weight (1701) of pentadigallyl glucose. The mixture is then diluted with an excess of ice water to complete precipitation of the tannate. The resulting precipitate is filtered off, washed thoroughly with ice water, and dried in a vacuum oven to yield the tannate as an amorphous solid.

Where a morphine alkaloid salt is the starting material, the free base may be liberated by addition of alkali metal hydroxide to alcohol or aqueous alcohol solution of the amine salt.

Example 1

Morphine tannate

3 grams of morphine base was dissolved in 30 milliliters of warm isopropyl alcohol containing 5 milliliters of ethanol. To this warm solution, there was added a warm solution of 4.5 grams of tannic acid N.F. in 15 milliliters of isopropyl alcohol. An immediate precipitate was formed. The mixture was cooled to at least room temperature, the tannate precipitate filtered off, washed with isopropyl alcohol and dried at 70 degrees Centigrade *in vacuo*. There was thus obtained 5.8 grams of cream-colored product. Recovery of morphine as its tannate can be increased by dilution with ice water; however, the undiluted filtrate can be used as a solvent for succeeding batches and morphine recovery improves with the repeated preparation.

The theoretical basic nitrogen content for morphine tannate having a ratio of morphine base to tannic acid of 4:1, 5:1 and 6:1 is calculated as 1.97 per cent, 2.24 per cent and 2.46 per cent respectively. The basic nitrogen found on analysis of the above product was 2.21 per cent. This indicates that the particular morphine tannate form was that having an approximate 5:1 ratio of morphine to tannic acid.

Example 2

Codeine tannate

To 2 grams of codeine sulphate suspended in 20 milliliters of methyl alcohol there was added 5 milliliters of 1-N NaOH in water. To this warm slurry there was added a warm solution of 2 grams of tannic acid N.F. in 20 milliliters of methyl alcohol. The mixture was diluted with water and ice and the precipitate filtered off and washed with water. The cream coloured product was dried at 70 degrees Centigrade *in vacuo* to yield 3.0 grams of codeine tannate. The theoretical basic nitrogen content for the 5:1 codeine to tannic acid proportion is 2.19 per cent, the found basic nitrogen was 2.0 per cent.

Example 3

Dihydrocodeine tannate

4.5 grams of dihydrocodeine base was dissolved in 100 milliliters of warm ethyl alcohol. To this warm solution, there was added a warm solution of 5.6 grams of tannic acid, N.F. in 50 milliliters of ethyl alcohol. This mixture was diluted with water and ice and the precipitate filtered off, washed with water, and dried at 70 degrees Centigrade *in vacuo*. There was thus obtained 8.5 grams of dihydrocodeine tannate in the form of a cream-colored solid. The thepretical basic nitrogen content for the 5:1 dihydrocodeine to tannic acid proportion is 2.18 per cent; the found basic nitrogen was 2.1 per cent.

The tannate salts of dihydrocodeinone, 6-methyldihydromorphinone, and ethyl morphine were also prepared by following the above procedures, and obtained as cream-colored solids.

The foregoing examples serve to illustrate the two alternative methods for preparing morphine alkaloid tannates. The tannates of the morphine alkaloids are cream-colored, amorphous solids which do not have true melting points but decompose at elevated temperatures. The morphine alkaloid tannates are compatible with the usual excipients and ingredients used in the formulation of oral pharmaceutical products provided as tablets, capsules or liquid suspensions.

The morphine and codeine tannates of the present invention were found to be effective agents in the relief of pain for extended periods of time without uncomfortable side effects. Similarly, codeine and dihydrocodeine tannates were found to extend the period of antitussive actions of these two alkaloids.

Morphine is customarily administered orally as the sulphate salt, the usual dose being 10 milligrams (rarely over about 20 milligrams) and the duration of its activity being about some 4 hours. The morphine tannate of the present invention has been administered in dosages of 30 milligrams, with the duration of its activity being about 8 hours, and sometimes even 12 hours, and dosages of 60 milligrams have been used on occasion. Dihydrocodeine tannate, for the relief of pain, has been administered in dosages of as much as 100 milligrams every 6—12 hours. Codeine tannate is also administered in dosages of 100 milligrams. These materials are usually supplied in capsule or tablet form. In general the morphine alkaloid tannates permit utiliz-

ation of the drugs for at least twice as long as the non-tannate form.

It should be noted in any comparison of the morphine alkaloid tannates with other forms of these alkaloids, that the tannate salts of the present invention contain roughly 43 per cent of the active ingredient morphine alkaloid.

It is to be understood that this invention is not to be limited to the exact compositions shown and described, as obvious modifications and equivalents along the lines suggested in this specification will be apparent to those skilled in the art.

WHAT WE CLAIM IS:—

1. A tannate of a morphine alkaloid as hereinbefore defined wherein the rates of morphine alkaloid to tannic acid is $5 \pm \frac{1}{2}:1$.

2. A tannate according to Claim 1 wherein the morphine alkaloid is morphine.

3. A tannate according to Claim 1 wherein the morphine alkaloid is codeine.

4. A tannate according to Claim 1 wherein the morphine alkaloid is dihydrocodeine.

5. The penta-morphine salt of penta-(digallyl)-glucose substantially free from other morphine-complexed tannins.

6. The penta-dihydrocodeine salt of penta-(digallyl)-glucose substantially free from other dihydrocodeine-complexed tannins.

7. The penta-codeine salt of penta-(digallyl)-glucose substantially free from other codeine-complexed tannins.

8. An oral sustained release composition in unit dosage form comprising penta-morphine-penta-(digallyl)-glucose substantially free from other morphine complexes of tannins and an excipient.

9. An oral sustained release composition in unit dosage form comprising penta-dihydrocodeine-penta-(digallyl)-glucose substantially free from other dihydrocodeine complexes of tannins and an excipient.

10. An oral sustained release composition in unit dosage form comprising penta-codeine-penta-(digallyl)-glucose substantially free from other codeine complexes of tannins and an excipient.

11. A process for the preparation of a morphine alkaloid tannate salt which comprises dissolving the alkaloid in an alcohol, adding for each molar equivalent 374 grams of tannic acid N.F. in a solution of the same alcohol, diluting the mixture with an excess of ice water to complete precipitation of the tannate, filtering off the resulting precipitate, washing thoroughly with ice water and drying in a vacuum oven to yield the tannate as an amorphous salt.

12. A process for the preparation of a morphine alkaloid tannate salt according to Claim 11, substantially as herein described with reference to any of the examples.

13. A morphine alkaloid tannate salt when prepared by a process as claimed in Claim 11 or 12.

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